


## REVIEW ARTICLE

# FISPGHAN statement on the global public health impact of metabolic dysfunction-associated steatotic liver disease

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**Abstract**

As rates of obesity rise worldwide, incidence of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly referred to as nonalcoholic fatty liver disease, is increasing, worsening the burden of healthcare systems. The council of the Federation of International Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) identified the topic of MASLD epidemiology, treatment, and prevention as a global priority issue to be addressed by an expert team, with the goal to describe feasible and evidence-based actions that may contribute to reducing MASLD risk. The FISPGHAN member societies nominated experts in the field. The FISPGHAN council selected and appointed members of the expert team and a chair. The subtopics included in this manuscript were chosen through a consensus of the experts involved. We review the epidemiology, natural history, and screening and management. We further expand to relevant public health measures aimed at MASLD prevention, including identifying interventions that could reduce risk factors (environmental and iatrogenic), optimize maternal and newborn health, and support healthier lifestyles for older children and adolescents on a local, national, and international scale. While recognizing that various aspects of population health and public policy can shape MASLD risk, we also review what we can do on an individual level to support our patients to reduce the significant burden of this ever rising disease in pediatrics.

**KEYWORDS**

childhood nutrition, maternal health, metabolic dysfunction-associated steatotic liver disease, nonalcoholic fatty liver disease, nutrition, obesity, public health

For affiliations refer to page 404.

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## 1 | INTRODUCTION

The rise in obesity in children worldwide is strongly associated with the rise in pediatric metabolic dysfunction-associated steatotic liver disease (MASLD).<sup>1</sup> Global childhood overweight and obesity prevalence accelerated to 18% in 2016, impacting 39 million children aged <5 years.<sup>2</sup> The rise in obesity and MASLD is multifactorial; understanding key drivers can guide prevention and public policy to reduce the burden of these chronic diseases worldwide.

## 2 | DEVELOPMENT OF THIS POSITION PAPER

The council of the Federation of International Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) identified the topic of MASLD epidemiology, treatment, and prevention as a global priority issue to be addressed by an expert team, with the goal to describe feasible actions that may contribute to reducing MASLD risk. The FISPGHAN member societies nominated experts in the field. The FISPGHAN council selected and appointed members of the expert team and a chair. The team worked together using phone conferences and digital communication. The subtopics included in this manuscript were chosen through a consensus of the experts involved. Each co-author drafted the first version of 1 section in the format of a narrative review, based on an electronic literature search performed by the respective author. These first drafts were then jointly revised by all authors, additional considerations and references were added, and these were combined to a final manuscript that was reviewed and approved by all authors. This manuscript was reviewed by the FISPGHAN council and approved with some modifications as a FISPGHAN position paper.

## 3 | GLOBAL DISEASE BURDEN AND NATURAL HISTORY

### 3.1 | Global epidemiology of pediatric MASLD

The worldwide incidence of pediatric MASLD increased from 19.34 in 1990 to 29.49 million in 2017.<sup>3</sup> MASLD is estimated to affect 7.6% of children, but rises to 34.2%–44.8% in those who are overweight/obese.<sup>4</sup>

Regional MASLD burden varies considerably in the general pediatric population, with the highest prevalence in South America (25%), followed by Oceania (10%), North America (8.5%), Asia (7%), North Africa (6.8%), and Europe (1.7%).<sup>4</sup> The prevalence in children with obesity is more comparable: South America 32.7%, North America 42.9%, Asia 46%, North Africa/

### What is Known

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global epidemic that continues to rise in pediatrics with many identified environmental and socioeconomic factors that increase risk at all stages of development in children and adolescents.

### What is New

- Identifying at-risk patients and preventative strategies are reviewed to support providers to mitigate risk of MASLD at all ages, beginning in the prenatal period.
- Guidance around minimizing these factors on a local, national, and international level are required to reduce risk and MASLD disease burden globally.

Middle East 36.5%, and Europe 34.7% (no data for Oceania).<sup>4</sup>

### 3.2 | Natural history of MASLD

Longitudinal follow-up in children with MASLD demonstrates bidirectional evolution, with some improving and others worsening. In a longitudinal United States (US) study of 122 children with MASLD who received standard lifestyle advice in placebo arms of clinical trials, improvement in metabolic dysfunction-associated steatohepatitis (MASH) or fibrosis occurred in 52%, in both in 20%, but only 2.4% achieved complete resolution.<sup>5</sup> Progression to MASH or fibrosis occurred in 36%, and in both in 11%.<sup>5</sup> Although fibrosis progressed in 23% of patients, no child developed cirrhosis. In a Dutch study that followed 51 adolescents with obesity over a mean of 10 years with serial hepatic imaging, 33% with baseline steatosis experienced resolution, but 6% developed increased Enhanced Liver Fibrosis<sup>®</sup> panel >9.8, suggesting advanced fibrosis.<sup>6</sup> Progression of severity associated with worsening metabolic risk, particularly diabetes.<sup>5,6</sup>

A heightened risk of developing adverse liver-related outcomes is a rising concern.<sup>1,7</sup> Childhood-onset MASLD has been associated with an increased risk of developing cirrhosis, liver failure, and early mortality in adulthood compared to the general population. One retrospective study in Minnesota (US) found a 13.8 times higher risk of dying or needing liver transplantation in adults with youth-onset MASLD versus age- and sex-matched controls.<sup>8</sup> Another study from Sweden found that childhood MASLD was associated with a 7.7% absolute risk of mortality in

adulthood, versus 1.1% in population-based controls, primarily due to cancer and cardiometabolic disease.<sup>9</sup> Adjusted mortality risk was fivefold higher with simple steatosis and 11-fold higher with MASH.<sup>9</sup>

### 3.3 | Environmental risk factors

The rapid globalization of the food supply chain has increased distribution and reduced the cost of ultra-processed, high-sugar/fructose, energy-dense food, and beverages worldwide.<sup>10</sup> Concurrently, technological innovations have increased sedentary behavior, reduced daily energy expenditure, and disrupted circadian rhythms, adversely affecting hormonal control of appetite and metabolic processes.<sup>10</sup> Low-resource countries and those that have experienced rapid economic development currently contribute the most to the global burden of childhood obesity.<sup>10</sup> Within low-resource countries, substantial heterogeneity exists in the prevalence of obesity in children, where malnutrition is concomitantly prevalent.<sup>10</sup>

Disruptions in the intestinal microbiome are associated with both obesity and MASLD risk. MASLD is associated with a reduction in anti-inflammatory activity and an increase in proinflammatory microbes.<sup>11</sup> Pediatric data have demonstrated lower alpha diversity, increased *Prevotella* species, serum ethanol levels, lipopolysaccharide biosynthesis, and alterations in lipid metabolism.<sup>12</sup> While diet is a major influence on the microbiome, prolonged or frequent childhood antibiotic, and acid suppressive therapy exposures have also been associated with an increased risk of developing obesity (both medication classes) and/or type 2 diabetes (antibiotics only), presumably through altered gut microbiome.<sup>13,14</sup>

Endocrine-disrupting chemicals (EDCs) or toxins, such as per-/polyfluorinated substances (PFAS), bisphenol A (BPA), phthalates, and polychlorinated biphenyls, have been increasingly linked to the development of MASLD.<sup>15</sup> EDCs are found in manufacturing and food packaging, persist across the lifespan, and have deleterious effects even at low exposures.<sup>15,16</sup> Fetuses, infants, and young children are more susceptible to metabolic perturbations owing to higher exposure per unit body weight and developmentally immature physiology. Prenatal exposure may promote epigenetic changes that alter metabolism and increase the risk of obesity, diabetes, and MASLD.<sup>16</sup> The Human Early-Life Exposome population-based cohort study of 1108 mother–child pairs from six European countries found that prenatal exposure to PFAS and several other EDCs significantly increased the risk for markers of liver injury around the age of 8 years.<sup>16,17</sup> Postnatally, chronic PFAS exposure has been associated with disruptions in glucose, amino acid, and bile acid metabolism, and with hepatocellular carcinoma.<sup>18,19</sup> BPA exposure has also

been linked to increased MASLD risk in Hispanic youth.<sup>20</sup>

## 4 | SCREENING AND MANAGEMENT IN MASLD IN CHILDREN: FOR THE PROVIDER

### 4.1 | Current screening recommendations

Screening remains challenging in MASLD due to the lack of international consensus, asymptomatic early-stage disease, and lack of validated noninvasive biomarkers for steatosis in children. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommends screening overweight and obese children (9–11 years of age).<sup>21</sup> However, several recent studies have highlighted that MASLD risk may begin earlier in childhood, with up to 30% of children under 6 years of age having elevated liver enzymes.<sup>22</sup> The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends screening obese children 3–10 years of age.<sup>23</sup>

Both the degree and distribution of adiposity are insufficient to detect hepatic steatosis.<sup>24</sup> While imaging evidence of steatosis is recommended for diagnosis of MASLD, current imaging modalities. Current NASPGHAN guidelines recommend using alanine aminotransferase (ALT) elevation to identify children at higher risk of more significant MASLD,<sup>21</sup> whereas ESPGHAN recommends both ultrasound (US) and ALT to increase detection of MASLD.<sup>23</sup> However, both methods have limitations. US has lower sensitivity to detect “mild” steatosis and increased echogenicity is not specific for steatosis.<sup>25</sup> US also has limited penetrance in individuals with severe obesity.<sup>25</sup> ALT also has compromised sensitivity and specificity for MASLD.<sup>26</sup> MASH with fibrosis can be present even with ALT < 50 IU/L. However, ALT > 80 IU/L is associated with higher risk of MASH.<sup>21</sup> Persistently ALT elevation of greater than two times the upper limit of normal (generally >44 U/L for girls and 52 U/L for boys) for over 3 months requires evaluation not only for MASLD, but for other etiologies such as infections, autoimmune, and metabolic disorders.<sup>21,23</sup> ALT thresholds, however, may vary regionally, with some countries reporting lower thresholds for upper limits of normal, which may modify decisions on when to initiate further evaluation.<sup>27–30</sup>

Noninvasive vibration-controlled transient elastography (VCTE) and magnetic resonance imaging (MRI) can be used to estimate steatosis (by US-derived controlled attenuation parameter [CAP] and MRI-derived proton density fat fraction) and fibrosis (by elastography-estimated liver stiffness) but may not be

widely available. Both CAP and VCTE scores require further validation in children at risk for MASLD.<sup>31</sup> While MRI has superior accuracy for quantifying hepatic steatosis and stiffness in overweight and obese children, its high cost precludes use for screening.

## 4.2 | Current treatment recommendations

The mainstay of treatment for pediatric MASLD are lifestyle interventions to achieve a healthy body composition and metabolism (Table 1).<sup>4,21</sup> Lifestyle interventions should be initiated by primary care providers (PCPs) as soon as MASLD is suspected or identified. Pediatric trials investigating specific dietary or exercise interventions are limited beyond the reduction in added sugars, which has been shown to rapidly improve hepatic steatosis.<sup>32</sup> Screening for metabolic comorbidities is recommended, but referral and treatment vary according to institutional practice and regional guidelines.<sup>4,21</sup> The utilization of a multidisciplinary approach is important to help achieve improvement in weight trajectory and improvement in ALT, which includes a dietician and even specialist in other disciplines where comorbidities may exist like endocrinologist, pulmonologist, and surgeons.<sup>33,34</sup>

Several medications may cause hepatic steatosis, including corticosteroids, certain chemotherapeutic

agents, and antiarrhythmic drugs.<sup>21</sup> Some psychotropic medications can lead to obesity and promote metabolic dysregulation, including MASLD.<sup>35,36</sup> Reducing exposure to these medications, when feasible, is recommended. Antibiotics and chronic acid suppression should be used judiciously, given adverse impacts on intestinal microbiome homeostasis, and potential link to increased risk of overweight/obesity and MASLD.

If advanced fibrosis develops or persists despite conventional lifestyle modifications, more intensive interventions should be considered (Table 2). High-dose vitamin E efficacy and long-term safety in children with MASLD remain unclear, nor does it improve the underlying metabolic dysregulation.<sup>37</sup> Several anti-obesity drugs have been approved by the Food and Drug Administration (FDA), European Medicines Agency, and other international agencies for children aged 12 years and older. These include orlistat, phentermine combined with topiramate, and glucagon-like peptide 1 (GLP-1) receptor agonists (liraglutide and semaglutide). GLP-1 receptor agonist trials in adults with MASLD have shown greater liver enzyme reduction and MASH resolution, but no significant fibrosis improvement.<sup>38</sup> However, the current high expense and extreme demand for GLP-1 receptor agonists have resulted in limited access. Furthermore, no dedicated clinical trials have investigated their efficacy in children with MASLD, thus if used to treat pediatric obesity, liver outcomes should be monitored closely.

**TABLE 1** Summary of treatment recommendations for MASLD in children.

Treatment(s)	Recommendations
Lifestyle recommendations	Focus on achieving and maintaining a healthy weight (low visceral adiposity) through consistent lifestyle modifications (detailed below) throughout the lifespan.
Dietary recommendations	Reduce intake of foods that are high in added sugars, refined carbohydrates, saturated and trans fats. Avoid consumption of sugar-sweetened beverages. Increase consumption of fruits and vegetables. A Mediterranean diet, which is high in fruits, vegetables, whole grains, and healthy fats, and lower in sugars, ultra-processed foods, and saturated/trans fats is often recommended based on data derived from adult studies.
Physical activity	Increase physical activity; aim for at least 60–180 min of moderate to vigorous activity daily and limit screen time activities to <2 hour per day in children >1–2 years of age. For children <2 years of age, no screen time is recommended.
Screening and treatment of comorbid conditions	
Diabetes mellitus	Regularly monitor for development of diabetes, through screening of fasting glucose and hemoglobin A1C levels. Refer to endocrinology or treat per current published guidelines.
Hypertension	Monitor blood pressure regularly using age and size-appropriate blood pressure cuffs and cut-offs; Refer to Cardiology or treat with antihypertensive medications per current published guidelines.
Dyslipidemia	Screen for elevated triglyceride, total cholesterol, and LDL cholesterol levels, and low HDL levels. Refer to lipid specialist or initiate treatment per current published guidelines.
Other metabolic conditions	Screen for signs and symptoms of polycystic ovarian syndrome, obstructive sleep apnea, lipodystrophy, as appropriate. Refer or manage as per published guidelines.

Abbreviation: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease.

**TABLE 2** When to refer to pediatric gastroenterology/hepatology and intensify treatment.

<b>When to refer to pediatric gastroenterology/hepatology</b>	
Persistent abnormal liver enzymes	Referral recommended if liver enzymes remain elevated despite weight loss or if they do not improve after consistent lifestyle interventions for 3–6 months. Liver enzymes (>80 IU/L) are associated with higher risk of MASH. Significantly elevated liver enzymes (>250 IU/L) can be seen in some children with MASH but also heighten concern for other causes of liver disease.
Signs of advanced liver disease	Physical findings of splenomegaly, ascites, or jaundice or laboratory signs of prolonged INR (>1.3 unresponsive to Vitamin K), thrombocytopenia, leukopenia, hypoalbuminemia, and cholestasis necessitate prompt referral.
Indications for liver biopsy	
Uncertain diagnosis	When noninvasive tests are not conclusive, exclusion of other liver diseases, persistent liver enzyme elevation despite lifestyle modification recommendations.
Assessment of liver damage	To evaluate the extent of fibrosis or steatohepatitis, if advanced liver disease is suspected.
Intensive treatment interventions	
Multidisciplinary lifestyle intervention	Multidisciplinary counseling administered by physicians, registered dietitians, exercise specialists, psychologists, or therapists with training in pediatric weight management is more effective in achieving clinically meaningful BMI Z score improvement. In children with MASLD and obesity, greater reduction in BMI z score has been associated with higher odds of MASH resolution in children.
Vitamin E therapy	Consider for nondiabetic children with biopsy-proven steatohepatitis, if no other options available. Recommended dose of 400 I.U. by mouth twice daily. Discontinue use if no improvement in 1–2 years.
Obesity medications	Approved medications include orlistat, phentermine-topiramate, and GLP1 receptor agonists (children with obesity ≥12 years of age); use in accordance with current pediatric guidelines and regional approval/availability. GLP1 receptor agonists are preferred for MASLD, based on data in adult trials that show greater improvement in MASH, but outcomes are uncertain regarding fibrosis improvement. No clinical trials have been conducted in children with MASLD—monitor liver outcomes closely.
Bariatric surgery	Consider in selected patients, e.g., adolescents with severe obesity and documented metabolic complications, following comprehensive evaluation.

Abbreviations: BMI, body mass index; GLP1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

Bariatric surgery is an established treatment for severe obesity in adolescents when significant comorbidities are present, including MASLD. Several studies demonstrate high-resolution rates of MASLD after bariatric surgery in children, but the long-term outcomes are unknown.<sup>39</sup> Endoscopic bariatric procedures are emerging treatments for obesity, but there have been no dedicated studies in children with MASLD.

## 5 | MOVING BEYOND TREATMENT TO PREVENTION

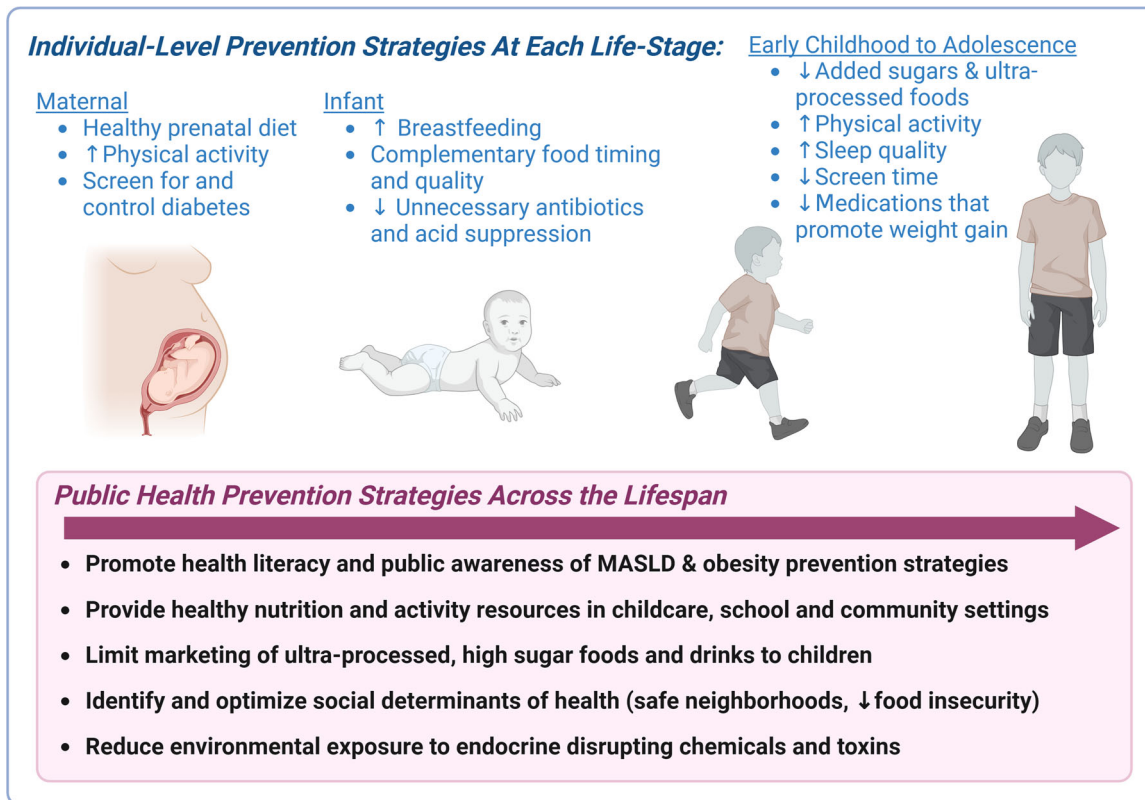
With the surge in MASLD and resultant social, economic, and healthcare burdens, preventative approaches are urgently needed. PCPs, as well as pediatric gastroenterologists and hepatologists, can provide counseling about modifiable factors linked to obesity and/or MASLD, raise awareness of public health burdens, and advocate for evidence-based public health interventions (Figure 1).

### 5.1 | Optimize maternal health

Several prospective prebirth cohort studies have identified modifiable maternal factors associated with an increased risk of MASLD in offspring, including maternal pre-pregnancy obesity and maternal diabetes (pregestational and gestational).<sup>40</sup> Higher maternal fiber intake and relative Mediterranean Diet Scores were associated with lower childhood MRI-assessed liver fat (at 5 years of age), whereas higher maternal total and added sugar intake and lower intake of green vegetables were associated with higher liver fat.<sup>41</sup> These associations highlight the importance of optimizing maternal diet and promoting greater physical activity before and during pregnancy, and the importance of screening and controlling maternal diabetes during pregnancy.<sup>42</sup>

### 5.2 | Promote early establishment of healthy nutrition and physical activity

Nutrition in the first 1000 days plays a significant role in determining cardiometabolic health and obesity, which



**FIGURE 1** MASLD prevention strategies should be implemented across the lifespan at both the individual level and through public health measures to reduce exposures known to be associated with increased risk of MASLD and/or obesity. Figure created with *BioRender.com*. MASLD, metabolic dysfunction-associated steatotic liver disease.

are linked to MASLD risk.<sup>43</sup> Breastfeeding provides optimal nutrition for growth and protects against excess weight gain in the first 2 years, and against obesity in later life.<sup>44</sup> Breastfed infants have improved regulation of calorie intake, both during the breastfeeding period and when solids are introduced.<sup>45</sup> Breastfeeding for  $\geq 6$  months during infancy has also been associated with a lower MASLD risk in adolescents.<sup>46</sup> Given the association between extended breastfeeding and reduced risk of MASLD, healthcare providers should ensure that mothers are counseled and supported in the initiation and maintenance of breastfeeding.

The timing and quality of complementary feeding can also affect long-term health and dietary habits. The early introduction of solids (<4 months of age) has been associated with a sixfold increased risk of obesity at 3 years in formula-fed infants.<sup>47</sup> Complementary feeding introduces new tastes and textures to help infants develop their oral motor feeding skills. Breastmilk also enhances early flavor exposure due to various volatile flavor compounds in contrast to the monotonous flavor of formula.<sup>48</sup> Infants and young children require varied and repeated exposure to new foods to increase acceptance. Parents and caregivers should be educated to read their child's hunger and satiety cues, and avoid excessive pressure or control at mealtimes, or use of food rewards.

Parents and caregivers should also be educated to limit access to ultra-processed foods, high salt intake, and sugar-sweetened beverages throughout childhood.

On a societal level, maternal leave policies should be designed to promote breastfeeding for a minimum of 6 months. Moreover, public health strategies should emphasize the importance of optimizing nutrition in the first 1000 days of life and tailoring recommendations to national and regional differences in diet practices.<sup>49</sup> Nutrition policy should extend to childcare and school environments, including limiting ultra-processed food and saturated/trans fats, and eliminating sugar-containing beverages from educational institutions.<sup>50</sup> Integrated strategies to regulate vending machines and marketed food within the school environment are in place in different countries, but more effort is required. In 2016, a World Health Organization global survey of school policies in 160 countries found 24% with standards to regulate food and beverage marketing and 18% with variable bans on vending machines in schools.<sup>51</sup> Nutrition education programs can also be integrated into educational curricula.<sup>52</sup> Policymakers should consider strategies to reduce fast-food outlets and improve the food environment near schools, as this may influence children's food selection.<sup>53</sup>

National and regional economic policies have also been shown to drive food consumption. Associations

**TABLE 3** Promote healthy physical activity early in life to establish healthy habits.

Age	Screen time	Activity recommendations
Infants < 1 year	None	Nonmobile infant—at least 30 min of tummy time spread throughout the day whilst awake
Toddlers 1–2 years	Ideally none No more than 1 hour/day Less is better	At least 180 min of any activity of any intensity, including moderate to vigorous intensity, throughout the day
Toddlers 3–5 years	No more than 1 hour/day Less is better	At least 180 min of any activity of any intensity, of which at least 60 min is moderate to vigorous intensity, throughout the day

between sweetened beverage taxes and decreasing soft drink purchases at the population level have been reported in various countries.<sup>54,55</sup> Similarly, revised agricultural policies and food labeling can assist in replacing trans fats and saturated fats with unsaturated fats through food chain.

Data from the 24-hour Movement Guidelines show that a comprehensive approach combining diet, physical activity, and sleep protects against obesity.<sup>56</sup> Children with increased sedentary behavior are more likely to have poor eating habits, whereas physically active children are more likely to have healthier diets.<sup>57</sup> With emerging evidence of an earlier onset of MASLD, establishing healthy activity habits should begin early in life with appropriate counseling for parents and caregivers (Table 3). Public health measures can expand childhood access to participation in sports, as part of school-based activities, competitions, or leisure, and invest in local and regional sports infrastructure.<sup>53</sup> Additional comprehensive community-level efforts to lower sedentary habits can be found in the MOVING framework, a tool designed to help policymakers, researchers, and civic organizations worldwide increase their levels of physical activity.<sup>58</sup>

### 5.3 | Identify and mitigate adverse social determinants of health (SDH)

Socioeconomic discrepancies contribute to an increased risk for MASLD. In adults, food insecurity is associated with disease severity but also with more advanced fibrosis.<sup>59</sup> In a longitudinal Finnish study of over 2000 individuals with follow-up into adulthood, those with high neighborhood socioeconomic disadvantage were more likely to be obese, have MASLD, and have diabetes when compared to those exposed to low neighborhood socioeconomic disadvantage.<sup>60</sup> Conversely, a study in Mexico showed that higher parental education, greater monthly food expenditure, and higher socioeconomic status were associated with an increased risk of MASLD,<sup>61</sup> highlighting the regional variation in socioeconomic factors and MASLD risk.

Screening for SDH in the clinic can identify needs and target resources to aid specific families. However,

modifying SDH risk factors at the population level will require greater societal and governmental investment, emphasizing the importance of advocating for greater awareness of MASLD.

### 5.4 | Reduce exposure to environmental toxins

Reducing exposure to toxins is challenging because of the widespread environmental contamination and long half-lives. Reducing the use of nonstick pans, stain-resistant materials, purchasing natural fibers in clothing, and BPA-free packaging can help reduce individual exposure, but broader public health measures and industrial regulations are needed to reduce environmental contamination. The ability of healthier dietary choices to mitigate these exposures requires further investigation in humans.

### 5.5 | Increase provider and public awareness

Education of PCPs to improve awareness of the increasing prevalence and associated health risks of MASLD is essential to ensure adherence to screening and treatment recommendations.<sup>62</sup> Increasing public awareness of MASLD is equally important for implementing preventive measures in early life. Health-promoting behaviors and habits are best developed at a young age, so appropriate education and support for parents and caregivers are key. This could involve public health campaigns sponsored by government and nongovernmental organizations, medical societies, and nonprofit organizations, and promoting health literacy.

Successful prevention of obesity cannot be achieved without an integrated multicomponent approach that targets community and socioeconomic factors. Community engagement is part of the sustainability framework necessary for obesity prevention and requires the attention of policymakers.

## 6 | CRITICAL RESEARCH GAPS: A NEED FOR GLOBAL COOPERATION

### 6.1 | Achieve global consensus in diagnostic criteria and nomenclature

Revisions in MASLD nomenclature were introduced in 2023 and have recently been endorsed in an international pediatric gastroenterology and hepatology societies statement.<sup>63</sup> The revised nomenclature is a major step forward, underscoring the pathophysiological metabolic dysregulation and emphasizing the high prevalence of comorbid conditions. Working toward increased global consensus on nomenclature will help promote greater public awareness and enhance the rigor of global databases and studies under a unifying definition.

### 6.2 | Broader global representation of epidemiology and natural history studies in children

Many studies regarding the natural history and long-term risk have been published in the United States or Europe.<sup>5,9</sup> Further international studies are needed, especially in regions where pediatric MASLD has escalated recently. In a recent analysis of the Global Burden of Disease Study data, countries on the Arabian Peninsula, African, and Asian countries bordering the Mediterranean Sea had the highest global prevalence of adolescent MASLD.<sup>64</sup> This may lead to an increase in end-stage liver disease and its complications. In addition to further study of the natural history of diverse populations, regional variation in genetic and environmental risk factors should be interrogated. The prognosis of nonobese children with MASLD must also be determined, as most prior longitudinal cohorts have predominantly included children who are overweight or obese.

Unlike other highly prevalent conditions, MASLD has not been the focus of any global or national public health improvement strategies.<sup>65</sup> Global registries of MASLD will be key in understanding the scope of the problem, increasing attention, and directing more resources to this overlooked health challenge to reduce disparity and improve outcomes.

### 6.3 | Urgent need for pediatric clinical trials with global participation

Pediatric MASLD has no approved pharmacotherapy. Despite numerous drugs in active clinical trials in adults with MASH and one new FDA-approved treatment for adults, extrapolation of these results to pediatric patients

is unclear because of varying histological phenotypes and severity of comorbidities. While studies on GLP-1 receptor agonists in adults are promising for achieving MASH resolution, dedicated pediatric studies are needed.<sup>38</sup> However, resmetirom has been recently approved in adults older than 18 years of age for treatment of MASLD with grade 2–3 fibrosis, which may bring new therapeutic options for children after pediatric clinical trials evaluate efficacy and safety of this therapy.<sup>66</sup>

Pediatric clinical trials of other treatments, including metformin, vitamin E, probiotics, and polyunsaturated fatty acids, have been limited and of varying rigor,<sup>4</sup> and face several unique challenges, including underdiagnosis, a heightened safety and regulatory clearance, and smaller patient populations with advanced disease ( $\geq$ stage 3 fibrosis).<sup>67</sup> Some of these challenges may be mitigated by collaborating to determine the natural history and improve study development.<sup>67</sup>

## 7 | SUMMARY

MASLD prevalence has surged in children worldwide and carries significant long-term morbidity. In addition to individual lifestyle risk factors, broader environmental and social factors have been linked to a heightened risk of childhood MASLD. These environmental and social determinants affect human health across the lifespan, highlighting the importance of increasing prevention efforts in clinical practice and implementing evidence-based public health interventions to reduce the burden of MASLD.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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